CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

POLYOXIN D ZINC SALT

Chemical Code # 5788, Tolerance # 52880

Original: November 5, 2002

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, unacceptable study, no adverse effect indicated[1]
Chronic toxicity, dog:	Data gap, no study submitted[1]
Oncogenicity, rat:	Data gap, no study submitted[1]
Oncogenicity, mouse:	Data gap, unacceptable study, no adverse effect indicated[1]
Reproduction, rat:	Data gap, no study submitted.[1]
Teratology, rat:	Data gap, no study submitted.[1]
Teratology, rabbit:	No data gap, acceptable study, no adverse effect
Gene mutation:	No data gap, acceptable study, no adverse effect
Chromosome effects:	No data gap, acceptable study, possible adverse effect
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	Not required at this time[1]

Toxicology one-liners are attached.
All record numbers through 015 1877781 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T021105
Original: M. Silva, 11/5/02

[1]New active ingredient, Polyoxin D Zinc Salt, submitted as a biochemical for non-food use. These studies are not required at this time.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

No Study submitted

CHRONIC TOXICITY, RAT

52880 - 015 187781 "Summary of Chronic Toxicity Study of Polyoxin D zinc salt in Rats," (Hori, M., Nippon University Medical Department, Tokyo, Japan; 1976) Polyoxin D zinc salt technical (12.2% pure) was fed in diet to ICR mice (36/sex/dose) at 0, 0.01, 0.1, 1.0 and 5% for 24 months. At 6, 12 and 18 months, 5 to 7/sex/dose were sacrificed. Chronic NOEL = 0.1%; 38.6 & 45.1 mg/kg/day for males and females, respectively (Rats at 5% had an aversion to the diet containing test material. Hemoglobin was decreased at $\geq$ 0.01% in females at 6 months. Total protein (> 1%), total cholesterol and ALP were statistically significantly decreased in females at 5% at 6 months. A/G ratio (5%) and ALP ($\geq$ 1.0%) at 12 months were statistically significantly decreased in females. Males at 12 months had statistically significantly increased BUN, decreased total cholesterol and ALP at 5%. Females had statistically significantly decreased ALP at $\geq$ 1% at 18 months. Females had statistically significantly decreased GPT at $\geq$ 1.0% at 24 months. Epididymal (24 months, seminal, according to the study) and kidney weights (6 months) were statistically significantly increased at 5%. Male thyroid weights were statistically significantly decreased at $\geq$ 1.0% at 18 months but not at 24 months. There were no consistent treatment-related changes in female organ weights.) Oncogenicity NOEL > 5% (There were no treatment-related effects on tumor incidence or histopathology.) No adverse effect indicated. Not acceptable or upgradeable. Supplemental data. M. Silva, 11/5/02.

CHRONIC TOXICITY, MOUSE

52880 - 015 187780 "Summary of Chronic Toxicity Study of Polyoxin D zinc salt in Mice," (Hori, M., Nippon University Medical Department, Tokyo, Japan; 1976) Polyoxin D zinc salt technical (12.2% pure) was fed in diet to ICR mice (30/sex/dose) at 0, 0.04, 0.4 and 4% for 24 months. At 6, 12 and 18 months, 5 to 7/sex/dose were sacrificed. NOEL = 0.04%; 34.78 and 30.86 mg/kg/day for males and females, respectively (Body weights of females were statistically significantly increased at 0.4% and decreased at 4% Polyoxin D zinc salt. Food consumption was increased by 12 and 16% at 0.4 and 4%, respectively. Total cholesterol was statistically significantly decreased in males at 12 months at $\geq$ 0.4% and in females at 24 months at 4%. Females had statistically significantly decreased absolute and relative kidney weights and increased relative uterine weights at 4% at 24 months. No treatment-related histological findings were reported in the text.) This study is not acceptable and not upgradeable. It contained summary data only and the Japanese translation was difficult to interpret. No adverse effect indicated. M. Silva, 11/5/02.

CHRONIC TOXICITY, DOG

No study submitted.

ONCOGENICITY, RAT

No study submitted

ONCOGENICITY, MOUSE

No study submitted

REPRODUCTION, RAT

No study submitted.

TERATOLOGY, RAT

No study submitted.

TERATOLOGY, RABBIT

** 52880 015 187779 "Teratology Study on Polyoxin D Zinc Salt (PSB) in Rabbits," (Yoshida, M.; Institute of Environmental Toxicology, Kaken Pharmaceutical Co., Ltd, Tokyo, Japan; Report #: 258-B; 3/18/93). Polyoxin D zinc salt (25.7 - 26.1% pure) was administered by gavage to mated Japanese White rabbit (JW-NIBS, 18/dose) at 0 (0.5% carboxymethylcellulose-Na aqueous), 50, 200 and 800 mg/kg during gestation days 6 - 18. Maternal NOEL = 200 mg/kg (There was a slight decrease in body weight and body weight gain after initial treatments. There were non-statistically significant decreases in # corpora lutea, # implants, implantation rate, # live fetuses and increased fetal mortality at 800 mg/kg, indicating that the treatment material was having a toxic effect.) Developmental NOEL > 800 mg/kg (There were no treatment-related effects at any dose.) Acceptable with no adverse effect. M. Silva, 11/5/02.

GENE MUTATION

** 52880 - 015 187776 "Reverse Mutation Test of PSB with Bacteria," (Yoshida, J.; Safety evaluation Laboratories, Kaken Pharmaceutical Co., Ltd.; Report #: SMT01, 2/16/94). Polyoxin D zinc salt technical (23.1% pure) was used on *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* WP2uvrA at 0 (1/20M EDTA), 156, 313, 625, 1250, 2500 and 5000 ug/plate (+/- S9 metabolic activation, 2 plates/dose) for 48 hours of treatment in a rangefinding test and a definitive reverse mutation test. After treatment with PSB solution either with or without S9, neither the formation of crystals nor growth inhibition of background lawn of test bacteria was observed even at the highest concentration of 5000 ug/plate. There was no treatment-related mutagenicity either with or without S9 in the 2 studies performed. The positive controls functioned as expected. No adverse effect. Acceptable. M. Silva, 10/28/02

** 52880 - 015 187778 "Mutagenicity Testing on Polyoxin D Zinc Salt in Microbial Systems: (1) Rec-Assay with *Bacillus subtilis* H-17 and M-45 (2) Reverse Mutation Tests With and Without a

Liver Metabolic Activation System Using Two Strains of *Escherichia coli* and Four Strains of *Salmonella typhimurium* and (3) Host-Mediated Assay with *S. typhimurium* G-46 in Mice," (Shirasu, Y., Moriya, M., Kato, K.; The Institute of Environmental Toxicology, Kaken Pharmaceutical Co., Ltd, Tokyo, Japan; Report #: 152-17-2; 6/76). Polyoxin D Zinc Salt (11.9% pure) was used as follows: Test 1: with *Bacillus subtilis* strains H-17 and M-45 at 0, 200, 1000 and 2000 ug/disk (spot test, 2 plates/dose), with no S9 (unacceptable); Test 2: with *Escherichia coli* strains WP2 hc*r*+ and WP2 hc*r*- and *Salmonella typhimurium* strains TA1535, TA1536, TA1537 and TA1538 at 0, 1000, 5000 and 10000 ug/plate (no S9, 2 plates/dose) and at 0, 100 and 1000 ug/plate (+/-S9, 2 plates/dose); Test 3: administered by gavage in 2 equal treatments to ICR male mice at 0 (5 mice), 2000 (6 mice) and 5000 mg/kg (4 mice) in a host mediated assay using *S. typhimurium* strain G-46 (3 plates/animal). There was no treatment-related increase in gene mutations in any test, compared to controls. The positive controls functioned as expected. Acceptable, with no adverse effect. M. Silva, 11/1/02.

CHROMOSOME EFFECTS

**** 52880 - 015 187777** "Studies on Chromosomal Aberration by Polyoxin D Zinc Salt in CHL Cells," (Yosida, J., Kaoru, K.; Safety Research Laboratories, Kaken Pharmaceutical Co., Ltd, Tokyo, Japan; Report #: KEN 87-04-03; 10/25/93). Polyoxin D zinc salt (PSB, 17.3% pure) was used on Chinese Hamster Fibroblast cells (CHL) at 0 (0.1 N-HCl), 0 (physiological saline), 0 (DMSO), 0.005, 0.01, 0.02 and 0.05 mg/kg with a 24 and 48 hour treatment (no S9 metabolic activation) and a 6 hour treatment followed by an 18 hour incubation (+S9). At termination, 50 cells/plate (duplicate cultures) were evaluated, for a total of 100/dose. At 24 hours 0.05 mg/ml (no S9), the frequency of cells with aberrations was 6% (gaps = 1%). At 48 hours (no S9), the frequency of polyploid cells was 5% and 6% at 0.005 and 0.01 mg/ml, respectively. Increases were not statistically significant, nor were they dose-related increases. Since PSB showed no dose-related increases after 48 hours, it is considered in the report to be cytotoxic to cells. Cells were therefore killed, rather than just having their propagation inhibited by aberrations. With S9, there was a slight increase in cells with aberrations (8% compared with 2% with saline) at 0.05 mg/ml. Possible adverse effect: Increased cells with chromosomal aberrations (+/-S9). Acceptable. M. Silva, 10/30/02

DNA DAMAGE

See 52880 - 015 18778, above.

NEUROTOXICITY

Not required at this time.